Spontaneous Hypoglycaemia After Pancreas Transplantation in Type 1 Diabetes Mellitus

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Hypoglycaemia is an important complication of insulin treatment in Type 1 diabetes mellitus (DM). Pancreas transplantation couples glucose sensing and insulin secretion, attaining a distinctive advantage over insulin treatment. We tested whether successful transplantation can avoid hypoglycaemia in Type 1 DM. Combined kidney and pancreas transplanted Type 1 DM who complied with good function criteria (KP-Tx, $n = 55$), and isolated kidney or liver transplanted non-diabetic subjects on the same immunosuppressive regimen (CON-Tx, $n = 14$), underwent 1-day metabolic profiles in the first 3 years after transplantation, sampling plasma glucose (PG) and pancreatic hormones every 2 hours. KP-Tx had lower PG than CON-Tx in the night and in the morning and higher insulin concentrations throughout the day. KP-Tx had lower PG nadirs than CON-Tx (4.40 ± 0.05 vs 4.96 ± 0.16 mmol l^{-1}, ANOVA $p = 0.001$). Nine per cent of KP-Tx had hypoglycaemic values (PG $\leq$3.0 mmol l^{-1}) in the profiles, both postprandial and postabsorptive, whereas none of CON-Tx did ($p < 0.02$). In conclusion, after pancreas transplantation, mild hypoglycaemia is frequent, although its clinical impact is limited. Compared to insulin treatment in Type 1 DM, pancreas transplantation improves but cannot eliminate hypoglycaemia. © **1998 John Wiley & Sons, Ltd.**

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Introduction

Even with optimal insulin therapy hypoglycaemia in Type 1 DM can rarely be completely avoided. Pancreas transplantation, which couples glucose sensing with insulin delivery, offers the great advantage of a more physiological, endogenous regulation of insulin delivery. It has been established that pancreas transplantation, combined with kidney grafting in uraemic Type 1 DM patients (KP-Tx), can near-normalize glucose metabolism;[1] improve protein[2] and lipid[3] metabolism; slow the progression of the Type 1 DM nephropathy[4,5] and neuropathy[6–9] and, according to some reports, retinopathy.[10–12] In theory, the restored glucose-to-insulin feedback and the quick dissipation of intravenously delivered insulin should also prevent episodes of relative or absolute hyperinsulinaemia that may predispose to severe hypoglycaemia. Since 'hypoglycaemia begets hypoglycaemia',[13] the avoidance of severe episodes could in turn normalize counterregulatory mechanisms and improve hypoglycaemia awareness.

One group reported that 3 Type 1 DM patients with a history of severe recurrent hypoglycaemia showed improved counterregulatory responses after pancreas transplantation[14,15] and another group reported that transplantation improves both hormonal[16,17] and hepatic[18] responses to hypoglycaemia. In contrast, we failed to demonstrate an improvement in the response to hypoglycaemia when a mild hypoglycaemic stimulus was applied.[19] Moreover, several groups reported that many pancreas recipients experience hypoglycaemic symptoms as well as overt hypoglycaemia,[19–23] although a systematic study of the prevalence and severity of hypoglycaemia after the transplant is lacking. This study was designed to test whether pancreas transplantation is

Abbreviations: CON-Tx control transplant recipients, KP-Tx recipients of simultaneous kidney and pancreas transplants, PG plasma glucose

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accompanied by a disappearance of hypoglycaemic episodes and to estimate the prevalence and the clinical impact of hypoglycaemia after pancreas transplantation in our institution. Since all pancreas transplanted patients are immunosuppressed, we chose as controls a group of non-diabetic patients who received a kidney or a liver transplant and were on a similar immunosuppressive regimen (CON-Tx).

Patients and Methods

Patient Selection

Only transplant recipients whose pancreas was functioning in the first 3 years after the transplant were included in this study. At 1 month and 1, 2 and 3 years after the transplant, subjects were insulin independent, with a postabsorptive plasma glucose <7.8 mmol l^{-1} and either HbA_{1c} <6.5 % or a postabsorptive C-peptide ≥ 0.66 nmol l^{-1}.

Pancreas and Kidney Recipients (KP-Tx)

Fifty-five Type 1 DM patients affected by end-stage uraemia who received a segmental or whole pancreas, along with a kidney from a cadaveric donor at the Ospedale San Raffaele between 1985 and 1995, were studied. In all cases, the pancreas had been anastomosed to the iliac vessels. The exocrine pancreatic juice was drained into the bladder when a whole pancreas was transplanted;[24] when a segmental pancreas was transplanted, the pancreatic duct was injected with neoprene.[25] Two-thirds of KP-Tx gave a history of severe hypoglycaemia prior to surgery.

Isolated Kidney or Liver Recipients (CON-Tx)

Nine non-diabetic subjects with end-stage nephropathy who had received a kidney from a cadaveric donor with identical renal transplantation procedure to KP-Tx and 5 non-diabetic subjects with liver cirrhosis associated with a small, non-metastatic hepatocarcinoma or with primary amyloidosis who had received an orthotopic liver from cadaveric donor[26] were studied.

Metabolic Profiles

One month and 1, 2 and 3 years after the transplant, the recipients were admitted to the hospital for a 24-h metabolic profile consisting of sampling plasma glucose, serum free-insulin, and C-peptide every 2 h. During the studies, the subjects received a standard isocaloric diet fractionated in a breakfast, lunch, and dinner chosen by the patient. They never fasted more than 13 h and they did not exercise during the study. Current therapy of the patients was recorded and plasma creatinine and glycated haemoglobin were measured each time. Data were analysed if the criteria for pancreatic function and at least 10 of the 12 points on the glucose profile were satisfied. On these criteria, 159 profiles of KP-Tx and 14 profiles of CON-Tx were included in the analysis.

Analytical Methods

Blood for the measurement of plasma glucose was placed in tubes containing Na-Fluoride and immediately centrifuged. The plasma was decanted and refrigerated at 4°C until assayed with a hexokinase method[27] (Boehringer Mannheim, Germany). The blood aliquots for free insulin and C-peptide were prepared as previously described and measured by RIA.[19]

Statistical Analysis

Values are expressed as means ± SEM, except when otherwise stated. All analysis were performed using the SAS program.[28] Comparisons between two means were performed by two-tailed *t*-test. Comparisons between two proportions were performed by χ^2 test and Fisher's exact test when appropriate. Two-way ANOVA was used to assess the effects of time and of the type of transplant. Multivariate analysis was used to assess the relationship between occurrence of hypoglycaemia and clinical parameters.

Results

Table 1 shows the clinical data of KP-Tx and CON-Tx. The groups were well matched for time elapsed from transplantation and immunosuppressive therapy, with the only difference that the liver recipients in CON-Tx received a slightly lower dose of steroids.

Time Course of Plasma Glucose, Free-insulin, and C-peptide

Figure 1(a) shows the mean courses of glucose, free insulin and C-peptide during the profiles. KP-Tx had significantly lower glucose concentrations at various times of the night and the morning, but similar concentrations after major meals. In contrast, KP-Tx had higher concentrations of free insulin throughout the day. The mean daily insulin concentrations were approximately double in KP-Tx than in CON-Tx (232 ± 9 vs 110 ± 35 pmol l^{-1}, ANOVA $p < 0.001$). However, C peptide concentrations were similar in the two groups except for a smaller C peptide response after breakfast and after lunch in KP-Tx.

Frequency of Hypoglycaemic Values

Individual glucose nadir concentrations are shown in Figure 1(b). In both groups, nadir concentrations

Table 1. Characteristics of the transplant recipients

	Pancreas and kidney recipients			Non-diabetic kidney or liver recipients
	All	PG <3.00 mmol l^{-1} in the profiles	PG >3.89 mmol l^{-1} in the profiles	
Number of recipients	55	5	37	14
Male/female	30/25	2/3	22/15	11/3
Duration of diabetes (yr)	25.6 ± 0.8	23.6 ± 2.5	26.2 ± 1.1	–
Age at Tx	38.1 ± 1.0	40.2 ± 3.1	38.3 ± 1.2	40.3 ± 2.8
Segmental/whole pancreas	16/39	1/4	11/26	–
Kidney/liver alone	–	–	–	9/5
Body mass index (kg m^{-2})	22.2 ± 0.4	22.3 ± 2	22.5 ± 0.4	23.6 ± 0.9
Plasma creatinine (μmol l^{-1})	1.42 ± 0.05	1.20 ± 0.20	1.43 ± 0.06	1.31 ± 0.09
Plasma albumin (g l^{-1})	–	–	–	41.6 ± 1.0
AST (U l^{-1})	–	–	–	24.0 ± 4.0
ALT (U l^{-1})	–	–	–	30.8 ± 6.0
Postabsorptive plasma glucose (mmol l^{-1})	5.00 ± 0.08	4.86 ± 0.31	5.12 ± 0.09	5.52 ± 0.20
Postabsorptive C-peptide (nmol l^{-1})	1.22 ± 0.06	1.26 ± 0.05	1.21 ± 0.08	1.04 ± 0.07
HbA_{1c}(%)	5.53 ± 0.09	5.46 ± 0.18	5.60 ± 0.13	6.11 ± 0.63
Prednisone (mg kg^{-1} day^{-1})	0.17 ± 0.01	0.17 ± 0.01	0.16 ± 0.01	0.12 ± 0.01[a]
Cyclosporin (mg kg^{-1} day^{-1})	5.50 ± 0.25	6.06 ± 0.75	5.47 ± 0.22	4.26 ± 0.41
Azathioprine (mg kg^{-1} day^{-1})	1.18 ± 0.08	1.10 ± 0.27	1.24 ± 0.10	1.18 ± 0.39
Number of recipients on β-blockers	16/39	1/4	8/29	6/8

[a] $p < 0.05$ vs pancreas and kidney recipients. For patients receiving methylprednisolone, the equivalent dose of prednisone was calculated.
AST = serum aspartate aminotransferase, ALT = serum alanine aminotransferase.

decreased similarly in the first 3 years from transplant (ANOVA $p < 0.05$), but each year the KP-Tx had lower values than CON-Tx (mean nadir 4.40 ± 0.05 vs 4.96 ± 0.16 mmol l^{-1}, ANOVA $p = 0.001$). None of the CON-Tx had a glucose concentration <3.89 mmol l^{-1}. In contrast, 18 KP-Tx had glucose concentrations <3.89 mmol l^{-1} and 6 had concentrations < 3.0 mmol l^{-1} (32.7 % and 9.1 % of all subjects, and 16.4 % and 3.1 % of all studies, respectively).

Relationship of Hypoglycaemic Values to Meals

Three of the 5 KP-Tx with glucose concentrations < 3.00 mmol l^{-1} had a postprandial glucose nadir (i.e. <6 h from the last meal). One of them also had a glucose concentration of 3.39 mmol l^{-1} at 8 a.m. the same day, suggesting that in this case the postprandial hypoglycaemic nadir did not reflect a true postprandial hypoglycaemia.

In KP-Tx the doses of prednisone were similarly tapered over the years both in the subjects with and in the subjects without hypoglycaemia in the profiles. None of the clinical parameters presented in Table 1 was found to be significantly related to the occurrence of hypoglycaemic values by multivariate analysis.

Discussion

In this study we have found that KP-Tx had lower plasma glucose than CON-Tx in the night and in the morning and achieved significantly lower glucose nadirs through the day. In contrast to CON-Tx, one-third of KP-Tx had values below 3.89 mmol l^{-1} and 9 % below 3.00 mmol l^{-1}. The first threshold (3.89 mmol l^{-1}) is the lower reference limit for normoglycaemia in adults in most hospital laboratories including ours. No real consensus exists on the lower limit for normoglycaemia, but none of the CON-Tx had lower values, suggesting that this limit is appropriate for them and counterregulatory responses of glucagon, adrenaline, and growth hormone in healthy subjects are initiated immediately below this threshold (3.66–3.83 mmol l^{-1}). Our data suggest that the KP-Tx have a defective regulation of lower glycaemic concentrations compared to CON-Tx. The clinical consequences of plasma glucose values between 3.00 and 3.89 mmol l^{-1} are uncertain. However, there is consensus that exposure to levels of ≤3.00 mmol l^{-1} has clinical consequences and we reserved the term 'hypoglycaemia' to values below 3 mmol l^{-1} to mean clinically significant hypoglycaemia. The fact that 9 % of KP-Tx had true hypoglycaemia in the profiles raises a second issue: what is the impact on the outcome of the recipients and what are the implications for pancreas transplantation as a therapy for hypoglycaemia-prone diabetic patients?

As regards the possible causes of hypoglycaemia in KP-Tx, both fasting and exercise[29,30] were excluded. None of the drugs consumed (prednisone, cyclosporine and β-blockers) could explain the difference with CON-Tx or the difference between KP-Tx with and without hypoglycaemia. Sex, age, duration of Type 1 DM, transplant duration, weight, BMI, segmental vs whole

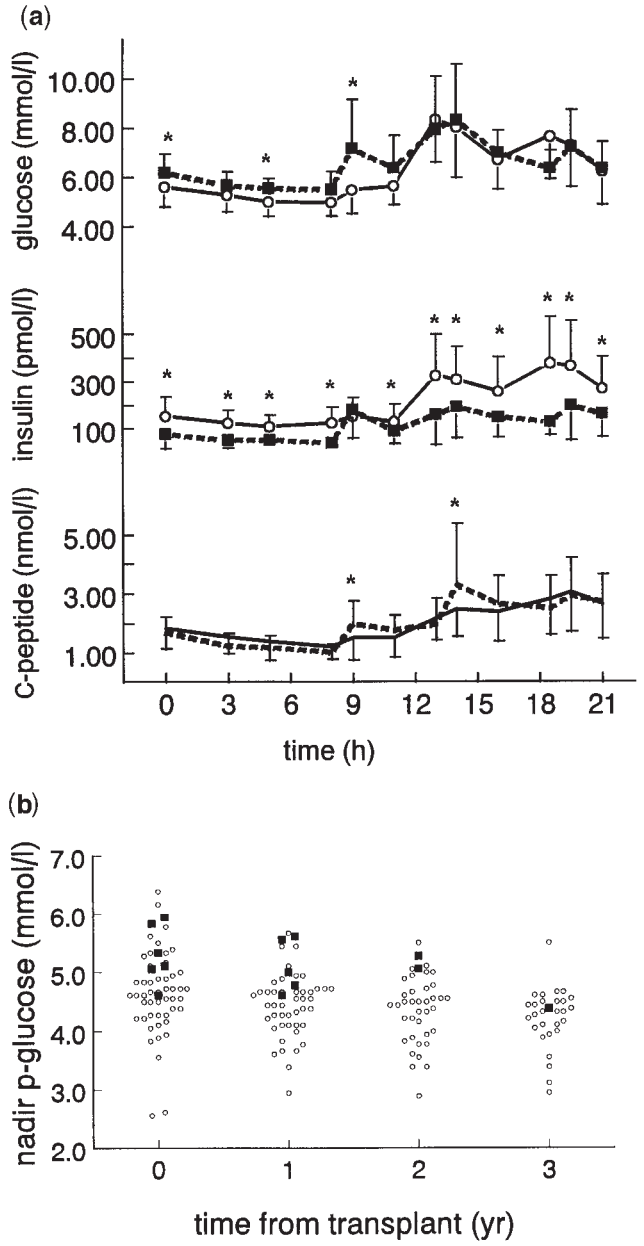

Figure 1. (a) Mean time course of plasma glucose, insulin, and C-peptide during the metabolic profiles in kidney and pancreas recipients (open circles) and in the control group of isolated kidney or liver recipients (closed squares). Kidney and pancreas recipients had lower glucose values in the night and in the morning, and higher insulin profiles throughout the day. Values are means ± SD. *Indicates $p < 0.05$ by ANOVA. (b) The individual values of daily glucose nadir tended to decrease in both groups in the years after transplant, however kidney and pancreas recipients had lower glucose nadirs than the control group (ANOVA $p < 0.001$)

pancreas graft, plasma creatinine and glycated haemoglobin were not related to risk of hypoglycaemia. We have found that pancreas recipients have a blunted glucagon response and an exaggerated suppression of endogenous glucose production during mild insulin-induced hypoglycaemia,[19] although Kendall *et al.*[17] found normal glucagon (but impaired adrenaline and noradrenaline) responses at various hypoglycaemic levels. However, a combination of mild defects in glucagon and adrenaline secretion after pancreas transplantation would not be surprising as pancreas denervation may prevent neuronal modulation of glucagon secretion in hypoglycaemia.[31] Furthermore, glucagon is secreted in the periphery after pancreas transplantation so the liver receives only a fraction of the glucagon pulses during hypoglycaemia. Finally, optimal glycaemic control and scrupulous avoidance of hypoglycaemia using exogenous insulin in Type 1 DM does not always normalize adrenaline responses to hypoglycaemia.[32,33]

It has been previously supposed that hypoglycaemia may be due to excessive peripheral insulin levels after feeding.[34] In our profiles, hypoglycaemia occurred both postprandially and postabsorptively, virtually excluding 'reactive' or 'postprandial' hypoglycaemia (which occurs typically within 4 h of a meal.[35] Peripheral insulin delivery with consequent hyperinsulinaemia may be important in the pathogenesis of hypoglycaemia. Chronic hyperinsulinaemia in insulinoma subjects causes a combination of erratic hypoglycaemia and insulin resistance,[36,37] two features that coexist to some degree also after transplantation.[1,2,38] In addition, insulin auto feedback is impaired in hypoglycaemia after transplantation[39] even though insulin dissipation is not really critical for the recovery from hypoglycaemia.[40] Finally, anti-insulin antibodies have been claimed to explain hypoglycaemia after transplantation,[41] although these were not demonstrated in the plasma of pancreas recipients.

What might be the clinical significance of the hypoglycaemia we have shown in our pancreas transplant recipients? The profiles sampled only 1 day per year, so we have probably underestimated the prevalence of hypoglycaemia after transplantation. Although our subjects were not instructed to report hypoglycaemic symptoms during the profiles, the fact that none did suggests that they may under-report hypoglycaemia in daily life. Symptom recognition during hypoglycaemia was reported to be restored by pancreas transplantation by one centre,[17] but it remains to be ascertained whether this would apply also to recipients with recurrent mild hypoglycaemia. Second, with the notable exception of a subject who had severe hypoglycaemic reactions in the third year after transplantation, most of our subjects reported that they were satisfied with the beneficial effect of pancreas transplantation on hypoglycaemia, because, despite persistence of symptoms, severe events dropped to zero after transplantation.[42] This is comparable to a study from Minnesota, in which most insulin-independent pancreas recipients reported that hypoglycaemic symptoms, although present, did not adversely affect their quality of life and only one patient experienced severe hypoglycaemia.[20] Overall, the improvement in quality of life after successful pancreas transplantation is striking, compared to other therapies for Type 1 DM, even though clinical surveillance and further studies are advisable for the rear individuals that seem to experience severe

hypoglycaemia after transplantation. Pancreas transplantation has been proposed for the tratment of Type 1 DM prone to severe hypoglycaemia.[43,44] This study shows that pancreas transplantation does not cure hypoglycaemia, although it also shows substantial benefit in patients prone to severe episodes.

In conclusion, this study has shown that Type 1 DM patients who receive a combined pancreas and kidney graft have lower glucose concentrations than non-diabetic recipients of isolated kidney or liver transplants, and continue to experience hypoglycaemia after the transplant, although the clinical impact of this is limited. It seems it is still not possible to cure Type 1 DM avoiding hypoglycaemia, although pancreas transplantation offers a valid option for the reduction of severe events related to hypoglycaemia.

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